Attachment to the Notice of Allowance

1. Applicants' amendments of 10/06/2009 are acknowledged. Claims 1, 8, 9, 26-31 have been amended, Claims 33-40 have been newly presented, and Claims 2-7, 10, 12-25 have been cancelled without prejudice or disclaimer as to the underlying subject mater.

Status of Claims

2. Claims 1, 8-9, 11, 26-40 are pending and under consideration.

Rejections Moot

3. Rejection of claims 2-4, 13 and 22-25 under 35 U.S.C.103 (a), made in paragraph 9 of the office action mailed 7/07/2009 is moot in view of cancellation of said claims.

4. Rejection of claims 1-7 under 35 U.S.C.103 (a), made in paragraph 10 of the office action mailed 7/07/2009 is moot in view of cancellation of said claims.

Rejections Withdrawn

5. Rejection of claims 1 , 8, 9, 11 and 26-32 under 35 U.S.C.103(a), made in paragraph 9 of the office action mailed 7/07/2009 is withdrawn in view of applicants' amendments of 10/06/2009.

6. Rejection of claim 1 under 35 U.S.C.103 (a), made in paragraph 10 of the office action mailed 7/07/2009 is withdrawn in view of applicants' amendments of 10/06/2009.

Deposit Rules

7. Newly submitted claim 39 recites a deposited organism registered number CNCM I-3005 under Budapest treaty. However, referrals in the specification missing a statement required. The details were communicated to attorney David Vanik Reg# 64,547 on a telephonic interview on 1/15/2010 to expedite prosecution. In response the attorney has submitted a Statement of Biological Deposit on 1/21/2010 which complies to deposit rules.

EXAMINER'S AMENDMENT

8. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with David Vanik Reg# 64,547 on a telephonic interview on 1/15/2010.

Please amend claims 1, 8, 9, 11, 26, 29, 30, 32, 33, 34, 35 and 39 as following:

Claim 1 (Currently amended): A method for producing ~~evolved~~ a microorganism~~s~~ wherein said microorganism is obtained by selection of a modified microorganism, having ~~an evolved~~ a modified methionine biosynthesis pathway for the biosynthesis of methionine by ~~the~~ metabolism of a simple carbon source and methylmercaptan as a source of sulfur, comprising:

a) generating a modified microorganism by inactivating, deleting, or inhibiting expression of ~~the~~ *met*E gene in an initial microorganism, wherein ~~the~~ ability of said modified microorganism to grow is impaired when grown on a minimal medium containing no methionine, S-adenosylmethionine, homocysteine or cystathionine;

b) culturing said modified microorganism obtained in step (a) on said minimal medium~~,~~ in the presence of methylmercaptan under selection pressure thereby allowing said modified microorganism to ~~evolve~~ proliferate through a methionine biosynthesis pathway to compensate for impaired growth; and

c) selecting ~~an evolved~~ said microorganism from step (b) able to grow on said minimal medium in ~~the~~ presence of methylmercptan,

wherein the methionine biosynthesis pathway ~~evolves~~ modifies such that methionine is produced by the metabolism of a simple carbon source and methylmercaptan as a source of sulfur thereby allowing said ~~evolved~~ microorganism to proliferate on said

minimal medium containing no methionine, S-adenosylmethionine, homocysteine or cystathionine.

Claim 8 (Currently amended): The method as claimed in claim 1, wherein said ~~evolved~~ microorganism possesses at least one ~~evolved~~ modified gene coding for ~~an evolved~~ a modified protein involved in the methionine biosynthesis pathway.

Claim 9 (Currently amended): The method as claimed in claim 8, comprising a step d) comprising the isolation of said ~~evolved~~ gene coding for ~~an evolved~~ a modified protein involved in the methionine biosynthesis pathway.

Claim 11(Currently amended): The method as claimed in claim 9, wherein ~~the evolved~~ said gene is introduced, into a production microorganism intended for the production of ~~the evolved~~ said protein.

Claim 26 (Currently amended): The method of claim 1, wherein said inactivating, deleting, or inhibiting expression of the *met*E gene is performed by directed mutation of said *met*E gene~~,~~ or directed modification of ~~a~~ ~~the~~ a promoter of said *met*E gene.

Claim 29 (Currently amended): The method of claim 1, wherein said ~~evolved~~ microorganism is a bacteria.

Claim 30 (Currently amended): The method of claim 1, wherein said ~~evolved~~ microorganism is an Escherichia sp.

Claim 32 (Currently amended): An evolved microorganism having ~~an evolved~~ a modified methionine biosynthesis pathway produced by the method of claim 1.

Claim 33 (Currently amended): The method of claim 8, wherein said gene coding for ~~an evolved~~ said protein involved in the methionine biosynthesis pathway is a mutated

*met*B gene with methionine synthase activity which allows for the direct conversion of O-succinyl-L-homoserine into L-methionine with methylmercaptan as a sulfur source.

Claim 34 (Currently amended): The method of claim 9, wherein said gene coding for ~~an evolved~~ said protein involved in the methionine biosynthesis pathway is a mutated *met*B gene with methionine synthase activity which allows for the direct conversion of O-succinyl-L-homoserine into L-methionine with methylmercaptan as a sulfur source.

Claim 35 (Currently amended): A method for ~~the~~ preparation of ~~evolved~~ modified strains of *E. coli* having ~~an evolved~~ a modified methionine biosynthesis pathway for the biosynthesis of methionine by ~~the~~ metabolism of a simple carbon source and methylmercaptan as a source of sulfur, comprising:
(a) generating a modified microorganism by inactivating, deleting, or inhibiting expression of ~~the~~ *met*E gene in an initial *E. coli* strain, wherein ~~the~~ ability of said modified microorganism to grow is impaired when grown on a minimal medium containing no methionine, S-adenosylmethionine, homocysteine or cystathionine,
b) culturing said modified microorganism obtained in step (a) on said minimal medium in ~~the~~ presence of methylmercaptan under selection pressure thereby allowing said modified microorganism to ~~evolve~~ proliferate through the methionine biosynthesis pathway to compensate for the impaired growth; and
c) selecting ~~an evolved~~ said *E. coli* strain from step (b) able to grow on said minimal medium in the presence of methylmercptan, said ~~evolved~~ microorganism comprising a mutated *met*B gene with methionine synthase activity and allowing the direct conversion of O-succinyl-L-homoserine into L-methionine with methylmercaptan as a sulfur source.

Claim 39. (Currently amended) The method of claim 35, wherein said ~~evolved~~ *E. coli* strain is strain *E. coli* 183 deposited at the Collection Nationale de Cultures de Microorganisms (CNCM) and registered under the number I-3005.

Allowable Subject Matter

9. Claims 1, 8, 9, 11 and 26-40 are allowed and renumbered 1-19 respectively.

The following is an examiner's statement of reasons for allowance: The claims are allowable over prior art. The closets prior art Richaud et al. (J. Biol. Chem., 268(36), 26827-26835(1993) fails to teach or fairly suggest the methods of Claims I, 8-9, 11, and 26-40. In particular, Richaud *et al.* does not teach or fairly suggest inactivating, deleting, or inhibiting expression of the *metE* gene. Richaud *et al.* fails to even mention the *metE* gene and does not describe methodology related to methionine biosynthesis.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol S. Shahnan-Shah whose telephone number is (571)-272-0863. The examiner can normally be reached on Mon, Wed 12:30-6:30 pm, Thur-Fri 12:30-4:30pm pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi can be reached on (571)-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert B Mondesi/
Supervisory Patent Examiner,
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1/28/2010